CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for: 071803

Trade Name : DESIPRAMINE HCL TABLETS USP 100MG

Generic Name: Desipramine HCL Tablets USP 100mg

Sponsor : Sidmak Laboratories, Inc.

Approval Date: May 29, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 071803

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 071803

APPROVAL LETTERS

ANDA 71-803

MAY 20 1997

Sidmak Laboratories, Inc.
Attention: Jairaj U. Mehta
17 West Street
P.O. Box 371
East Hanover, NJ 07936

Dear Sir:

This is in reference to your abbreviated new drug application dated January 16, 1987, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Desipramine Hydrochloride Tablets USP, 100 mg.

Reference is also made to your amendments dated April 5 and 25, 1991, May 8, 1991; August 30, 1993; June 24, 1996; March 5, and May 22, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Desipramine Hydrochloride Tablets, 100 mg to be bioequivalent and, therefore, therapeutically equivalent to those of the listed drug (Norpramin® Tablets, 100 mg, of Hoechst Marion Roussel, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

5/29/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 071803

FINAL PRINTED LABELING

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are generally advisable, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. Aggressive support therapy of cardiac, neurologic, or acid-base disturbances may be necessary.

The initial phase of therapy in a tricyclic antidepressant overdose should be devoted to protection of the patient's airway, stabilization of the vital signs, establishing an intravenous line, obtaining an ECG, and initiating continuous cardiac monitoring, and maintaining renal output. It should be remembered that rapid deterioration of vital signs, seizures, respiratory failure, and ventricular arrhythmias are common during the first twenty-four hours after ingestion.

Ventricular arrhythmias and intraventricular conduction abnormalities may respond to administration of sodium bicarbonate to correct the metabolic acidosis. During alkalinization, the patient's electrolytes and renal function must be closely monitored with frequent laboratory determinations. Arrhythmias may be treated with standard antiarrhythmic therapy (e.g., lidocaine). Physostigmine may be used with caution to reverse severe cardiovascular abnormalities or coma; too rapid administration may result in seizures.

If the patient is hypotensive, supportive measures (e.g., intravenous fluids) should be used. Vasopressor agents may be used with caution if necessary. If the patient develops seizures, intravenous diazepam may be used. In addition, longer acting anticonvulsants (e.g., barbiturates) may be necessary for repetitive seizures.

Once the patient is stabilized, gastric lavage with a large bore orogastric tube should be used to evacuate the stomach. The physician must be prepared to protect the airway by endotracheal intubation if seizures or loss of consciousness occur prior to completion of the lavage procedure. Because of the potential for rapid onset of life-threatening events, emesis should not be used to empty the stomach. Activated charcoal (as single or repeated doses) in a water slurry should be given by mouth or instilled through the lavage tube.

Additional information regarding treatment of overdosage may be available from poison control centers.

DOSAGE AND ADMINISTRATION: Not recommended for use in children.

Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients compared to hospitalized patients, who are closely supervised. Dosage should be initiated at a low level and increased according to clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a period of time and should be at the lowest dose that will maintain remission.

Usual Adult Dose: The usual adult dose is 100 to 200 mg per day. In more severely ill patients, dosage may be further increased gradually to 300 mg/day if necessary. Dosages above 300 mg/day are not recommended.

Dosage should be initiated at a lower level and increased according to tolerance and clinical response.

Treatment of patients requiring as much as 300 mg should generally be initiated in hospitals, where regular visits by the physician, skilled nursing care, and frequent electrocardiograms (ECG's) are available.

The best available evidence of impending toxicity from very high doses of desipramine hydrochloride is prolongation of the QRS or QT intervals on the ECG. Prolongation of the PR interval is also significant, but less closely correlated with plasma levels. Clinical symptoms of intolerance, especially drowsiness, dizziness and postural hypotension, should also alert the physician to the need for reduction in dosage. Plasma desipramine measurement would constitute the optimal guide to dosage monitoring.

Initial therapy may be administered in divided doses or a single daily dose.

Maintenance therapy may be given on a once-daily schedule for patient convenience and compliance.

Adolescent and Geriatric Dose: The usual adolescent and geriatric dose is 25 to 100 mg daily. Dosage should be initiated at a lower level and increased according to tolerance and clinical response to a usual maximum of 100 mg daily. In more severely ill patients, dosage may be further increased to 150 mg/day. Doses above 150 mg/day are not recommended in these age groups.

Initial therapy may be administered in divided doses or a single daily dose.

Maintenance therapy may be given on a once-daily schedule for patient convenience and compliance.

HOW SUPPLIED: Desipramine Hydrochloride Tablets, USP:

25 mg - Light yellow, round, sugar-coated tablets in bottles of 100 and 1000.
Imprint: SL 36

50 mg - Light green, round, sugar-coated tablets in bottles of 100 and 1000.
Imprint: SL 437

75 mg - Light orange, round, sugar-coated tablets in bottles of 100 and 1000.
Imprint: SL 438

100 mg - Peach, round, sugar-coated tablets in bottles of 100 and 1000.
Imprint: SL 439

150 mg - White, round, sugar-coated tablets in bottles of 100 and 1000.
Imprint: SL 440

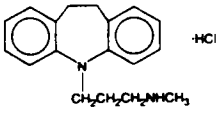
Dispense in a tight container as defined in the USP with a child-resistant closure.
Store at controlled room temperature 15°-30°C (59°-86°F). Keep tightly closed.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by
SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

P08-0436 Rev. 4/95 L

DESCRIPTION: Desipramine hydrochloride is an antidepressant drug of the tricyclic type and is chemically 5*H*-Dibenz[*b*,*f*]azepine-5-propanamine, 10, 11-dihydro-*N*-methyl-, monohydrochloride.



·HCl

$CH_2CH_2CH_2NHCH_3$

$C_{18}H_{22}N_2 \cdot HCl$ M. W. 302.85

P08-0436

DESIPRAMINE HYDROCHLORIDE TABLETS, USP

Rev. 4/95 L

Each tablet for oral administration contains 25 mg, 50 mg, 75 mg, 100 mg or 150 mg desipramine HCl. Inactive ingredients include carnauba wax, colloidal silicon dioxide, confectioners' sugar, anhydrous lactose, magnesium stearate, methylparaben, polyethylene glycol, povidone, pregelatinized starch, purified iron oxide, shellac, silicon dioxide, sodium starch glycolate, stearic acid, sucrose, talc, titanium dioxide, FD&C Yellow #6 (25 mg, 75 mg, 100 mg), D&C Yellow #10 (25 mg, 50 mg, 100 mg), and FD&C Blue #1 (50 mg).

CLINICAL PHARMACOLOGY: Mechanism of Action: Available evidence suggests that many depressions have a biochemical basis in the form of a relative deficiency of neurotransmitters such as norepinephrine and serotonin. Norepinephrine deficiency may be associated with relatively low urinary 3-methoxy-4-hydroxyphenyl glycol (MHPG) levels, while serotonin deficiencies may be associated with low spinal fluid levels of 5-hydroxyindoleacetic acid.

While the precise mechanism of action of the tricyclic antidepressants is unknown, a leading theory suggests that they restore normal levels of neurotransmitters by blocking the re-uptake of these substances from the synapse in the central nervous system. Evidence indicates that the secondary amine tricyclic antidepressants, including desipramine, may have greater activity in blocking the re-uptake of norepinephrine. Tertiary amine tricyclic antidepressants, such as amitriptyline, may have greater effect on serotonin re-uptake.

Desipramine hydrochloride is not a monoamine oxidase (MAO) inhibitor and does not act primarily as a central nervous system stimulant. It has been found in some studies to have a more rapid onset of action than imipramine. Earliest therapeutic effects may occasionally be seen in 2 to 5 days, but full treatment benefit usually requires 2 to 3 weeks to obtain.

Metabolism: Tricyclic antidepressants, such as desipramine hydrochloride, are rapidly absorbed from the gastrointestinal tract. Tricyclic antidepressants or their metabolites are to some extent excreted through the gastric mucosa and reabsorbed from the gastrointestinal tract. Desipramine is metabolized in the liver and approximately 70% is excreted in the urine.

The rate of metabolism of tricyclic antidepressants varies widely from individual to individual, chiefly on a genetically determined basis. Up to a thirty-six-fold difference in plasma level may be noted among individuals taking the same oral dose of desipramine. In general, the elderly metabolize tricyclic antidepressants more slowly than do younger adults.

Certain drugs, particularly the psychostimulants and the phenothiazines, increase plasma levels of concomitantly administered tricyclic antidepressants through competition for the same metabolic enzyme systems. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant. Other substances, particularly barbiturates and alcohol, induce liver enzyme activity and thereby reduce tricyclic antidepressant plasma levels. Similar effects have been reported with tobacco smoke.

Research on the relationship of plasma level to therapeutic response with the tricyclic antidepressants has produced conflicting results. While some studies report no correlation, many studies cite therapeutic levels for most tricyclics in the range of 50 to 300 nanograms per milliliter. The therapeutic range is different for each tricyclic antidepressant. For desipramine, an optimal range of therapeutic plasma levels has not been established.

INDICATIONS AND USAGE: Desipramine hydrochloride is indicated for relief of symptoms in various depressive syndromes, especially endogenous depression.

CONTRAINDICATIONS: Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hyperpyretic crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When desipramine hydrochloride is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Desipramine hydrochloride should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

WARNINGS:

1. Extreme caution should be used when this drug is given in the following situations:
   a. In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction.
   b. In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug.
   c. In patients with thyroid disease or those taking thyroid medication because of the possibility of cardiovascular toxicity, including arrhythmias.
   d. In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold.
2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds.
3. USE IN PREGNANCY: Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or women of childbearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive.
4. USE IN CHILDREN: Desipramine hydrochloride is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established. (See **ADVERSE REACTIONS, Cardiovascular**.)
5. The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
6. In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage.

PRECAUTIONS:

1. It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly.
2. If serious adverse effects occur, dosage should be reduced or treatment should be altered.
3. Desipramine therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates.
4. The drug may cause exacerbation of psychosis in schizophrenic patients.
5. Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs.
6. Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated.
7. Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered.
8. If desipramine hydrochloride is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of desipramine and benzodiazepines (e.g., chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of desipramine.
9. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma levels of the tricyclic antidepressants (see **CLINICAL PHARMACOLOGY, Metabolism**). Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant.
10. There have been greater than twofold increases of previously stable plasma levels of tricyclic antidepressants when fluoxetine has been administered in combination with these agents.
11. This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride.
12. Both elevation and lowering of blood sugar levels have been reported.
13. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression.

Drug Interactions: ***Drugs Metabolized by P450 2D6:*** The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7 to 10% of Caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be co-administered with another drug known to be an inhibitor of P450 2D6.

ADVERSE REACTIONS:

Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when desipramine hydrochloride is given.

Cardiovascular: hypotension, hypertension, palpitations, heart block myocardial infarction, stroke, arrhythmias, premature ventricular contractions, tachycardia, ventricular tachycardia, ventricular fibrillation, sudden death.

There has been a report of an "acute collapse" and "sudden death" in an eight-year (18 kg) old male, treated for two years for hyperactivity. There have been additional reports of sudden death in children. (See **WARNINGS**, USE IN CHILDREN.)

Psychiatric: confusional states (especially in the elderly) with hallucinations, disorientation, delusions, anxiety, restlessness, agitation, insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurologic: numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus.

Anticholinergic: dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure; constipation, paralytic ileus; urinary retention, delayed micturition, dilatation of urinary tract.

Allergic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

Hematologic: bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue, hepatitis, jaundice (simulating obstructive), altered liver function, elevated liver function tests, increased pancreatic enzymes.

Endocrine: gynecomastia in the male, breast enlargement and galactorrhea in the female, increased or decreased libido, impotence, painful ejaculation, testicular swelling; elevation or depression of blood sugar levels, syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Other: weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; fever; alopecia; elevated alkaline phosphatase.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

OVERDOSAGE:

Signs Symptoms, and Laboratory Findings: Signs and symptoms of toxicity with tricyclic antidepressants most often involve the cardiovascular and central nervous systems. Overdosage with this class of drugs has resulted in death. Within a few hours of ingestion, the patient may become agitated, restless, confused, delirious or stuporous, and then comatose. Mydriasis, dry mucous membranes, vomiting, urinary retention, and diminished bowel sounds may occur. Hypotension, shock, respiratory depression, and renal shutdown may ensue. Generalized seizures, both early and later after ingestion, have been reported. Hyperactive reflexes, hyperpyrexia, and muscle rigidity can occur. ECG evidence of impaired conduction and serious disturbances of cardiac rate, rhythm, and output may occur. The duration of the QRS complex on ECG may be a helpful guide to the severity of tricyclic overdose. Physicians should be aware that relapses may occur after apparent recovery.

Oral LD_{50}: The oral LD_{50} of desipramine is 290 mg/kg in male mice and 320 mg/kg in female rats.

Toxic and Lethal Doses/Plasma Levels: In humans, doses at 10 to 30 times the usual daily dosage have been considered within the lethal range. The lethal dose for children and geriatric patients would be lower than that for the general adult population. Serious adverse events in general are more frequently associated with plasma levels in excess of 1000 ng/mL.

Dialysis: After overdosage, low plasma desipramine concentrations are found because of the drug's large volume of distribution in the body. Forced diuresis and hemodialysis are, therefore, ineffective in removing tricyclic antidepressants.

Treatment: There is no specific antidote for desipramine overdosage, nor are there specific phenomena of diagnostic value characterizing poisoning by the drug.

P08-0436

NDC 50111-439-03

Desipramine HCl Tablets, USP 100 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 Tablets

Sidmak® LABORATORIES, INC.

MAY 29 1997

EACH TABLET CONTAINS:
Desipramine HCl, USP ..... 100 mg

Dispense in a tight container as defined in the USP with a child-resistant closure.

Store at controlled room temperature 15°-30°C (59°-86°F). Keep tightly closed.

USUAL DOSAGE: See package insert.

N 3 50111-439-03 0

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

Control No.:
Exp. Date:

NDC 50111-439-01

Desipramine HCl Tablets, USP 100 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Sidmak LABORATORIES, INC.

EACH TABLET CONTAINS:
Desipramine HCl, USP ..... 100 mg

Dispense in a tight container as defined in the USP with a child-resistant closure.

Store at controlled room temperature 15°-30°C (59°-86°F). Keep tightly closed.

USUAL DOSAGE: See package insert.

Control No.:
Exp. Date:

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

N 3 50111-439-01 6

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 071803

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 6

2. ANDA # 71-803

3. NAME AND ADDRESS OF APPLICANT

Sidmak Laboratories, Inc.
17 West Street
P.O. Box 371
East Hanover, NJ 07936

4. LEGAL BASIS for ANDA SUBMISSION

Innovator Drug: Norpramin, Merrel Dow; No patents or exclusivity remaining.

5. SUPPLEMENT(s) - None

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Desipramine HCl Tablets USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

1.16.87: Original submission
6.9.87: Amendment #1
8.13.87: Amendment #2
9.22.87: Amendment #3
9.30.87: Amendment #4
5.13.91: Amendment #5
10.30.91: Amendment #6
6.30.92: Amendment #7
5.9.95: Amendment #8
6.27.96: Amendment
3.5.97: Amendment

FDA:

1.28.87: Acknowledgment letter
1.28.87: Acknowledgment letter
5.29.87: 1st NA letter by Maria Shih/J Meyer (Branch I) with original formulation containing as drug substance. This was not used for Bio study.

11.5.87: 2nd NA letter by Maria Shih/J Meyer (Branch I) with original formulation containing as drug substance. This was not used for Bio study.

10.31.91: Respond or withdraw letter

9.11.91: NA letter (labeling)

2.26.92: 3rd NA letter by D. James/P. Schwartz (Branch VI) with the 1st revised formula containing deleting and other and using the drug substance source - This batch was used for Bio study.

9.25.92: 4th NA letter (Major) by U Venkataram/F Fang (Branch VII) with the 1st revised formula containing deleting and other and using the drug substance source - This batch was used for Bio study.

11.17.95: 5th NA letter By L Tang/J Simmons (Branch VII) with the 2nd revised formula containing a reduction in solvent emissions (isopropyl alcohol) and a change in the quantity of coating excipients by using the drug substance source and container/closure system changes.

2.12.97: 6th NA letter

10. PHARMACOLOGICAL CATEGORY

Anti-depressive

11. Rx or OTC

R_x

12. RELATED IND/NDA/DMF(s)

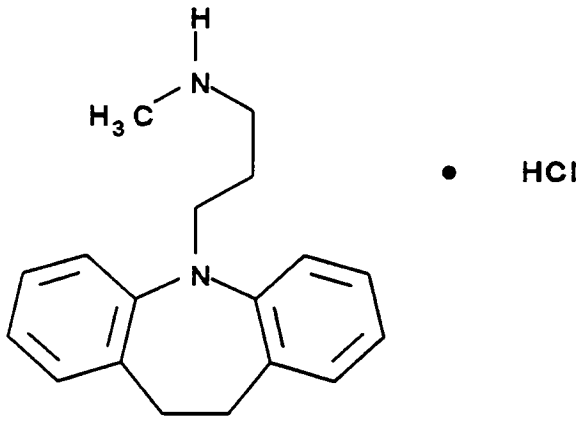
13. DOSAGE FORM Tablets

14. POTENCY 100 mg

15. CHEMICAL NAME AND STRUCTURE

Desipramine Hydrochloride USP

$C_{18}H_{22}N_2.HCl$; M.W. = 302.85



10,11-Dihydro-5-[3-(methylamino)propyl]-5*H*-dibenz[*b*,*f*]-azepine monohydrochloride. CAS [58-28-6]

16. RECORDS AND REPORTS

N/A

17. COMMENTS

Q: 1. Please submit the comparative dissolution data between lot 90-023T (old formulation) and lot 95-018T (new formulation).

A: OK (see Exhibit 1).

Q: 2. Due to changes in the process, procedure, and formulation (isopropyl alcohol) as well as quantity of coating excipients, please request a waiver of in vivo bioequivalence studies from the Division of Bioequivalence.

A: OK (see Exhibit 2).

Status:

a. **EER:** Satisfactory

Request for applicant

by L Tang on 10-18-95 and found acceptable on 12-19-95. Updated and pre-approval EER was requested on 1-10-97 by L. Tang and found acceptable on 4-7-97.

b. **MV** (method validation):

Active drug substance and drug dosage form are both compendial items per USP 23. Samples will not be requested for testing by FDA labs.

c. **Bio-Review**: Satisfactory for the formulation revision

Study acceptable for 100 mg product. 150 mg granted waiver. Reviewer - M. Makary, dated 7-31-91. The acceptable Bio-study and waiver lots are from the old formulation. The comparative dissolution data between lot 90-023T (old formulation) and lot 95-018T (new formulation) and a waiver of the in vivo bioequivalence studies, based on the additional revisions that have been made to the formulation have been reviewed and found acceptable per M. Makary reviewed on 3-24-97.

d. **Labeling review:** Satisfactory

Satisfactory per D. Konigstein and A. Payne reviewed on 9-19-95.

e. **DMFs: satisfactory**

DMF was reviewed by L Tang and found satisfactory on 10-18-95 and 1-14-97.

18. CONCLUSIONS AND RECOMMENDATIONS

APPROVAL

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 3-25-97 and 4-7-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 071803

BIOEQUIVALENCE REVIEW(S)

7/31/91

Desipramine HCl
100 mg Tablet
ANDA # 71-803
Reviewer: Moheb H. Makary
WP MM71803

Sidmak Laboratories, Inc.
East Hanover, NJ
Submission Date:
April 25, 1991

Review Of AN Amendment

The firm submitted information in this amendment pertaining to the determination of Desipramine in human plasma by [redacted] regarding the bio-study conducted on Sidmak's Desipramine HCl, 100 mg Tablet. This bio-study has already been reviewed by the Division of Bioequivalence (submission dated April 5, 1991). No further action is needed.

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

Concur:

Ramakant M. Mhatre, Ph.D.
Acting Deputy Director
Division of Bioequivalence

MMakary/5-13-91/WP MM71803

cc: ANDA # 71-803 original, HFD-600 (OGD), HFD-630, HFD-604 (Hare), HFD-658 (Mhatre-Makary), HFD-22 (Hooton), Drug File.

7/31/91

Desipramine HCl
100 mg Tablet
ANDA # 71-803
71803SDW.591

Sidmak Laboratories, Inc.
East Hanover, NJ
Submission Date:
May 13, 1991

Review Of An Amendment To A Bioequivalence Study

The firm submitted dissolution data on those tablets used in the bio-study conducted on Sidmak's Desipramine HCl Tablets 100 mg (lot # 90-023T) and Merrell Dow's Norpramin[R] Tablets 100 mg (lot # 8942YF). Also included in this amendment are dissolution data for Sidmak's Desipramine HCl Tablets 150 mg (lot # 90-022T) and Merrell Dow's Norpramin Tablets 150 mg (lot # 8645YD). These data have already been reviewed by the Division of Bioequivalence in the Sidmak's Desipramine HCl bio-study (submission dated April 5, 1991). No further action is needed.

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

Concur.

Ramakant M. Mhatre, Ph.D.
Acting Deputy Director
Division of Bioequivalence

MMakary/6-21-91/wp 71803SDW.591

cc: ANDA # 71-803 original, HFD-600 (OGD), HFD-630, HFD-604 (Hare), HFD-658 (Mhatre-Makary), HFD-22 (Hooton), Drug File.
1

7/31/91

Desipramine HCl
100 mg Tablet
ANDA # 71-803
71803SD.591

Sidmak Laboratories, Inc.
East Hanover, NJ
Submission Date:
May 8, 1991

Review Of An Amendment To A Bioequivalence Study

The firm submitted copy of a page which was inadvertently omitted from the submission on April 25, 1991. The April 25, 1991 submission contained a copy of the addendum to the bio-study (volume 1.2; submitted April 5, 1991). This bio-study has already been reviewed by the Division of Bioequivalence. No further action is needed.

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

Concur:

Ramakant M. Mhatre, Ph.D.
Acting Deputy Director
Division of Bioequivalence

MMakary/6-24-91/wp 71803SD.591

cc: ANDA # 71-803 original, HFD-600 (OGD), HFD-630, HFD-604 (Hare), HFD-658 (Mhatre-Makary), HFD-22 (Hooton), Drug File.

7/31/91

Desipramine HCl Tablets
ANDA # 71-803 (100 mg)
ANDA # 71-804 (150 mg)
Reviewer: Moheb H. Makary
WP M71803

Sidmak Laboratories, Inc.
East Hanover, NJ
Submission Date:
April 5, 1991

Review Of A Bioequivalence Study, Dissolution Data And Request For Waiver

I. Objective:

The firm has submitted a bioequivalence study for its 100 mg Desipramine HCl Tablet, and dissolution data to compare the test product relative to Merrell Dow's Norpramin 100 mg Tablet for approval. The firm has also requested waiver of *in vivo* bioequivalence study requirements for its 150 mg Tablet.

II. Introduction:

Desipramine HCL is an antidepressant drug of tricyclic type. The mechanism of action is thought to involve the drug's ability to block the re-uptake of neurotransmitters in the CNS, thus restoring their levels to normal. Desipramine HCl is rapidly absorbed from the gastrointestinal tract, metabolized in the liver to active metabolite 2-hydroxydesipramine which undergoes conjugation with glucuronic acid. The rate of metabolism of Desipramine HCl varies widely from individual to individual, chiefly due to genetics determined basis. Up to a thirty-sixfold difference in plasma level may be noted among individuals taking the same oral dose of desipramine. Upon single oral dosing, peak plasma level occurs 4-8 hours post-dose. The drug is 90% plasma protein bound, and approximately 70% is excreted in the urine. The distribution phase may last as long as 8-12 hours. The biologic half-life is 22 hours. The drug is marketed by Merrell Dow in 6 tablet strengths (Norpramin; 10, 25, 75, 100 and 150 mg). It is also marketed by Rorer Pharm in 2 capsule strengths (Pertefrane; 25 and 50 mg).

III. Background:

Sidmak Laboratories, Inc., has approved ANDA's for the 25, 50 and 75 mg strengths of Desipramine HCl Tablet.

IV. Study Details: (Protocol # 900398)

Study site:

Sponsor: Sidmak Laboratories, Inc.
East Hanover, NJ
USA

Investigators:

Study design:	Comparative, randomized, single-dose, 2-way crossover bioavailabililty study.
Subjects:	Thirty male volunteers were enrolled in the study, with 29 completing.
Selection criteria:	Male, healthy, 18-45 years of age, weighing at least 60 kg, within 15% of their ideal weights (Metropolitan Life Insurance Company, 1983), only medically healthy subjects with clinically normal laboratory profiles were enrolled in the study.
Laboratory Tests:	Hematology, serum chemistry, urinalysis and HIV-AIDS test were performed prior to the initial dose.
Exclusion criteria:	History of allergy to the test medication or to any tricyclic antidepressant drugs. Any evidence of organ dysfunction. History of serious gastrointestinal, hepatic, renal, respiratory, psychological, thyroid, cardiovascular or hematological diseases. History of asthma, glaucoma, urinary retention, prostate enlargement with symptoms, depression, or personal or family history of seizure disorders, alcoholism or drug abuse.
Prohibitions:	Medication (including OTC products, and MAO inhibitors) was prohibited for 14 days preceding the study. Xanthine and caffeine containing products were prohibited for 24 hours before dosing and throughout the period of sample collection.
Food and fluid intake:	Single oral 1-tablet dose, 100 mg Desipramine HCl of either test or reference product was administered with 240 mL of water following an overnight fast. Standard meals at 4 and approximately 9 hours after drug administration and at appropriate times thereafter.
Blood samples:	Blood samples were collected in vacutainers containing EDTA before dosing (2x10 mL) and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24,

36, 48, 72, and 96 hours after dosing (1x10 mL each).

Dose and treatment:

(a) Test Product: 1x100 mg Desipramine HCl Tablet (Sidmak Laboratories, Inc.), lot # 90-023T, expiry date 11/92, batch size Tablets.

(b) Reference Product: 1x100 mg Desipramine HCl Tablet (Merrell Dow Norpramin^{R}), lot # 8942YF, expiry date 6/93.

Washout period: 14 days

Assay Methodology

Statistical Analysis

Three-way analyses of variance was performed with subjects, periods and drugs (i.e. formulations) as factors, and sequence as a between-subjects factor for the pharmacokinetic parameters. 90% confidence intervals (two one-sided t test procedure) and ratio analyses was calculated for the parameters AUC, AUCinf and Cmax.

V. In Vivo Results:

Thirty male volunteers were enrolled in the study, 29 subjects completed the study. Subject # 4 was withdrawn from the study following an episode of vomiting shortly after period 2 dosing. All

enrolled subjects were judged to be medically healthy based on medical history, physical examination and clinical laboratory tests. To monitor subject safety, sitting blood pressure and heart rate were determined pre-dose and at approximately 2, 4, 6, and 8 hours after drug administration. No safety problems were encountered.

The plasma Desipramine concentrations and pharmacokinetic parameters are summarized in Table I.

Table I

Mean Plasma Desipramine Concentrations And Pharmacokinetic Parameters Following An Oral Dose Of 100 mg Desipramine HCl Tablet

Time (hr)	Test Sidmak's Desipramine HCl Lot # 90-023T ng/mL	(CV%)	Reference Norpramin (Merrell Dow) Lot # 8942YF ng/mL	(CV%)
0.0	0.00	(00.0)	0.00	(00.0)
0.5	0.88	(141.9)	0.17	(255.5)
1.0	5.43	(79.5)	3.21	(81.2)
2.0	20.46	(50.3)	18.78	(63.3)
3.0	29.11	(40.1)	28.73	(52.9)
4.0	32.22	(39.1)	31.37	(39.2)
5.0	34.42	(36.7)	35.09	(38.3)
6.0	38.29	(36.3)	39.28	(35.3)
7.0	38.36	(36.9)	39.82	(35.3)
8.0	36.23	(35.9)	38.66	(37.0)
10.0	33.82	(40.6)	32.90	(36.6)
12.0	30.31	(40.1)	32.44	(39.9)
16.0	24.60	(49.4)	24.90	(43.5)
24.0	18.53	(56.2)	19.29	(54.5)
36.0	13.90	(75.1)	14.43	(69.3)
48.0	10.25	(94.0)	10.69	(85.6)
72.0	5.22	(126.4)	5.57	(117.0)
96.0	3.80	(158.3)	2.92	(161.0)

	Test	Reference	T/R	90% CI
AUC (ng.hr/mL)	1276.8	1282.2	0.99	93.3, 105.9%
AUCinf(ng.hr/mL)	1586.8	1599.2	0.99	93.1, 105.4%
Cmax (ng/mL)	40.6	42.3	0.96	90.1, 102.1%
Tmax (hr)	6.76	6.76		
Kel (1/hr)	0.037	0.037		
Half-life (hr)	18.55	18.61		

1. The plasma desipramine levels rose rapidly and reach a peak in 7 hour for both the test and reference products (Table I). The plasma profiles were comparable between Sidmak's product and Merrell Dow's Norpramin at all time points except at 0.5, 1 and 12 hour time points when the differences were found to be statistically significant (p LT 0.05), which were in agreement with lower dissolution rate of the reference product relative to the test product at 15 and 30 minutes Table II.

2. Sidmak's test product had an AUC of 1276.8 ng.hr/mL and AUCinf of 1586.8 ng.hr/mL which were in both cases 99% of the reference product values. The 90% confidence intervals of the test means were within the acceptable range of 93.1-105.4%.

3. The Cmax of Sidmak's test product was 4% lower than reference product value. The difference was not statistically significant, and the 90% confidence interval of the test mean was within the acceptable range, 90.1-102.1% of the reference mean.

4. The Tmax, Kel and Half-life were comparable between the test and the reference products (Table I).

Statistical Evaluation:

Analysis of variance (ANOVA) indicated that there were significant differences between the two phases in the AUC and AUCinf. These differences might be a result of equal carry over for the test and reference product from one phase to the second phase which has no significant effect on the study. No sequence effect was observed.

VI. Formulations:

Sidmak's comparative formulations for Desipramine HCl Tablet, 100 mg and 150 mg are shown in Table III.
The formulation for the 150 mg strength is proportionally similar to the 100 mg strength of the test product which underwent bioequivalent testing.

VII. In Vitro Dissolution Testing:

Method:	USP XXII, apparatus II (paddle) at 50 rpm.
Medium:	900 mL of 0.1N HCl
Number of Tablets:	12
Specification:	NLT n 45 minutes
Test Products:	Sidmak's Desipramine HCl
	100 mg Tablet, lot # 90-023T
	150 mg Tablet, lot # 90-022T
Reference Products:	Merrell Dow's Norpramin
	100 mg Tablet, lot # 8942YF
	150 mg Tablet, lot # 8645YD

All products dissolved greater than n 45 minutes and met FDA specification Table II.

VIII. Comments:

1. The firm's in vivo bioequivalence study using 100 mg Tablets is acceptable.

2. Waiver of in vivo bioequivalence study requirements for the test 150 mg Tablet product may be granted based on the acceptable bioequivalence study conducted on 100 mg Tablet, the acceptable dissolution testing and proportional formulation.

IX. Recommendations:

1. The bioequivalence study under fasting condation conducted by Sidmak Laboratories, Inc., on its Desipramine HCl, 100 mg Tablet, lot # 90-023T, comparing it to Merrell Dow's Norpramin, 100 mg Tablet has been found acceptable by the Division of Bioequivalence. The study demonstrates that Sidmak's Desipramine HCl 100 mg Tablet is bioequivalent to the reference product, Norpramin 100 mg Tablet.

2. The dissolution testing conducted by Sidmak Laboratories, Inc., on its Desipramine HCl 100 mg and 150 mg Tablets, lot # 90-023T and 90-022T, respectively, is acceptable.
The formulation for the 150 mg strength is proportionally similar to the 100 mg strength of the test product which underwent bioequivalence testing. Waiver of in vivo bioequivalence study requirements for the 150 mg Tablet of the test product is granted. The Division of Bioequivalence deems the Desipramine HCl, 150 mg Tablet, manufactured by Sidmak Laboratories, Inc., to be bioequivalent to the Norpramin, 150 mg Tablet, manufactured by Merrell Dow Pharmaceuticals.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP XXII apparatus II (paddle) at 50 rpm. The product should meet the following specification:

> Not less than of the labeled amount of Desipramine HCl in the dosage form is dissolved in 45 minutes.

4. From the bioequivalence point of view, the firm has met the requirements of in vivo bioequivalence and in vitro dissolution testing and the application is approvable.

The firm should be informed of the above Recommendations.

Moheb H. Makary, Ph.D.
Division of Bioequivalence
review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRF

Concur: _____ Date: 7/23/91
Shrikant V. Dighe, Ph.D.
Director
Division of Bioequivalence

MMakary/7-18-91/wp M71803

cc: ANDA # 71-803 original, HFD-600 (OGD), HFD-630, HFD-604 (Hare), HFD-658 (Mhatre,Makary), HFD-22 (Hooton), Drug File.

Drug (Generic Name): Desipramine Hcl Tablet Firm: Sidmak Laboratories, Inc.
Dose Strength: ~~100 mg, 150 mg~~
ANDA # 71-827 (100 mg) Submission Date: April 5, 1991
71-804 (150 mg)

Table II - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXII Basket ___ Paddle ✓ RPM 50 No. Units Tested: 12

Medium: 0.1N HCl Volume: 900 ml

Reference Drug; (Manuf.): Norpramine (Merrell Dow)

Assay Methodology: ___

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.) (Hr.)	Sidmak Test Product Mean % Dissolved	Range	(CV)	Merrell Dow Reference Product Mean % Dissolved	Range	(CV)
	Lot # 90-022T			Lot # 8947 4E		
	Strength (mg) 100			Strength (mg) 100		
15	90.2		(8.4)	36.4		(12.5)
30	94.0		(2.7)	73.9		(10.1)
45	99.7		(1.8)	98.2		(5.9)
60	99.5		(1.5)	103.1		(1.6)
___	___	___	( )	___	___	( )
	Lot # 90-022T			Lot # 8645 4D		
	Strength (mg) 150			Strength (mg) 150		
15	59.8		(22.2)	38.7		(11.1)
30	90.5		(10.2)	75.7		(7.2)
45	94.9		(6.6)	98.0		(2.8)
60	96.9		(3.7)	100.5		(0.4)
___	___	___	( )	___	___	( )

Table III

SIDMAK LABORATORIES, INC.

COMPARATIVE COMPOSITION PROPORTIONALITY

DESIPRAMINE HYDROCHLORIDE TABLETS

INGREDIENTS	100MG mg/unit	%/unit	150MG mg/unit	%/unit
A. CORE				
Desipramine HCl USP	100.00	29.41	150.00	28.85
Lactose NF				
Starch NF				
Povidone USP				
Sodium Starch Glycolate NF				
Colloidal Silcon Dioxide NF				
Stearic Acid NF				
Magnesium Stearate NF				
B. COATING EXCIPIENTS				
Sucrose NF				
Methylparaben NF				
Povidone USP				
Polyethylene Glycol NF				
Talc USP				
Colloidal Silicon Dioxide NF				
Starch NF				
Confectioners Sugar				
Titanium Dioxide USP				
Carnauba Wax NF				
Yellow Wax NF				
*FD&C Yellow #6 Lake				
*D&C Yellow #10 Lake				
A. TOTAL WEIGHT OF CORE TABLETS				
B. TOTAL WEIGHT OF COATING EXCIPIENTS				
TOTAL WEIGHT OF THE TABLET	**340.00mg/tab**		**519.86mg/tab**	

*Desipramine HCl Tablets 100mg ONLY

ANDA 71-803; 100 mg
71-804; 150 mg

FEB - 5 1997

Sidmak Laboratories, Inc.
Attention: Arun D. Kulkarni
17 West Street
P.O. BOX 371
East Hanover NJ 07936

Dear Sir:

Reference is made to the request for waiver from *in vivo* bioequivalence requirements, submitted on June 24, 1996, for Desipramine Hydrochloride Tablets USP, 100 mg and 150 mg.

The Office of Generic Drugs has reviewed the waiver request and has found that the dissolution testing for Desipramine Hydrochloride Tablets USP, 100 mg and 150 mg Tablets, lot #95-018T and 95-019T, respectively, is not acceptable for the following reason:

> The comparative dissolution of the test products (revised and original formulations) should be tested as part of the same experiment. The dissolution data on the original formulation of the test product submitted in November 1990, is not acceptable. If no samples of the original tablet formulations are available, the use of Norpramin® Tablets, 100 mg and 150 mg, as the reference products would be acceptable.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Rabindra Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DN

JAN 28 1997

Desipramine HCl Tablets
100 mg and 150 mg
ANDA #71-803 (100 mg)
ANDA #71-804 (150 mg)
Reviewer: Moheb H. Makary
WP 71803D.696

Sidmak Laboratories, Inc.
East Hanover, NJ.
Submission Date:
June 24, 1996

Review of Amendments

I. Objective:

The firm has submitted these amendments with the revised formulations (a change in the quantity of coating excipients) for its products desipramine HCl, 100 mg and 150 mg Tablets. The firm had submitted an acceptable bioequivalence study on its desipramine HCl, 100 mg Tablets and a waiver was granted for the 150 mg strength (submission dated April 5, 1991). Desipramine HCl, 100 mg and 150 mg Tablets have not been approved by the Agency per chemistry deficiencies.

The firm has submitted comparative dissolution testing data for its revised formulations (submitted in these amendments) and for the original approved formulations (submitted in the April 5, 1991 submission).

II. Formulations:

Comparison of the proposed formulations for desipramine HCl 100 mg and 150 mg with the formulations in Sidmak's original formulations (April 5, 1991) on its desipramine HCl 100 mg and 150 mg is shown in Tables I and II.

III. Comment:

The formulations for the core tablets have not changed for desipramine HCl 100 mg and 150 mg Tablets. The proposed changes in quantity of coating excipients are similar to the changes requested by the firm and were found acceptable by the Division of Bioequivalence for its approved desipramine HCl 75 mg, 50 mg and 25 mg Tablets (submissions dated June 7, 1993, ANDA #71-802, 71-801 and 71-800).

IV. Deficiency Comment:

The dissolution testing for desipramine HCl, 100 mg and 150 mg Tablets lot #95-018T and 95-019T, respectively, is not acceptable. For the test products (the revised formulation) the firm submitted dissolution testing dated 4/95 and for the original formulations (reference product) 11/90. The comparative dissolution testing for the test and reference products should be tested at the same time. If the firm no longer has samples of the original Tablets (formulations), the use of Norpramin® 100 mg and

150 mg tablets as the appropriate reference products would be acceptable.

V. Recommendation:

The dissolution testing conducted by Sidmak Laboratories, Inc., on its desipramine HCl, 100 mg and 150 mg Tablets lot #95-018T and 95-019T, respectively, is unacceptable and the waivers are denied for reason cited in deficiency comment.

The firm should be informed of the above recommendation.

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

Date: 1/23/97

Concur: _____ Date: 1/28/97
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

MMakary/1-22-97 wp 71803D.696
cc: ANDA #71-803, 71-804, original, HFD-658 (Makary), Drug File, Division File.

Table III In Vitro Dissolution Testing

Drug (Generic Name): Desipramine HCl
Dose Strength: 100 mg and 150 mg Tablets
ANDA No.:71-803, 71-804
Firm: Sidmak Laboratories, Inc.
Submission Date: June 24, 1996
File Name: 71803D.696

I. Conditions for Dissolution Testing:

USP 23 Basket: Paddle:X RPM: 50
No. Units Tested: 12 Tablets
Medium:900 mL of 0.1N HCl
Specifications: NLT of the labeled amounts of Desipramine is dissolved in 45 minutes.
Reference Drug: Norpramin
Assay Methodology

II. Results of In Vitro Dissolution Testing: Desipramine

Sampling Times (minutes)	Test Product Lot # 95-018T Strength(mg) 100			Reference Product Lot # 90-023T Strength(mg) 100		
	Mean %	Range	%CV	Mean %	Range	%CV
10	91		6.4	90.2		8.4
30	100		1.6	99.0		2.7
45	101		1.1	99.7		1.8
60	101		1.0	99.5		1.5

Sampling Times (minutes)	Test Product Lot # 95-019T Strength(mg) 150			Reference Product Lot # 90-022T Strength(mg)150		
	Mean %	Range	%CV	Mean %	Range	%CV
10	31		34.3	60		22
30	78		6.5	91		7.2
45	93		2.8	98		2.8
60	96		2.0	101		0.9

1a0'a ** (Revised for mulation)

COMPONENTS/COMPOSITION STATEMENT

Desipramine Hydrochloride Tablets, USP 150 mg
Formula Code: 440-03

	Ingredients	mg/unit
CORE		
1)	Desipramine HCl Powder USP	150.00
2)	Anhydrous Lactose NF	
3)	Pregelatinized Starch NF	
4)	Povidone USP	
5)	Isopropyl Alcohol USP **	
6)	Sodium Starch Glycolate NF	
7)	Colloidal Silicon Dioxide NF	
8)	Stearic Acid NF	
9)	Magnesium Stearate NF	
SUGAR COATING		
1)	Povidone USP	
2)	Polyethylene Glycol 600	
3)	Sucrose NF	
4)	Methylparaben NF	
5)	Talc USP	
6)	Silicon Dioxide NF	
7)	Pregelatinized Starch NF	
8)	Purified Water USP **	
9)	Confectioner's Sugar NF	
10)	Titanium Dioxide USP	
11)	Carnauba Wax NF	
12)	Fine Black Printing Ink (Solids) *	
13)	Thinner (Q.S.) (for printing ink) **	
	TOTAL OF THE SUGAR COATING	

*

TOTAL WEIGHT OF THE TABLET **537.11**

** Does not appear in the finished product

*** Amounts of coating ingredients are theoretical and may vary ±10%.

ANDAs 71-803
71-804

Sidmak Laboratories, Inc.
Attention: Jairaj U. Mehta
17 West Street
P.O. BOX 371
East Hanover NJ 07936

MAR 28 1997

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Desipramine Hydrochloride Tablets USP, 100 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

for Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MAR 24 1997

Desipramine HCl Tablets
100 mg and 150 mg
ANDA #71-803 (100 mg)
ANDA #71-804 (150 mg)
Reviewer: Moheb H. Makary
WP 71803D.397

Sidmak Laboratories, Inc.
East Hanover, NJ.
Submission Date:
March 5, 1997

Review of Amendments

I. Objective:

The firm has replied to the reviewer's comments made in the review of the June 24, 1996 submissions (an amendments with revised formulations for its products desipramine HCl, 100 mg and 150 mg Tablets).

II. Comment:

The firm was asked to submit comparative dissolution testing data for its products (the revised and original formulations) being tested as part of the same experiment. If no samples of the original tablet formulations are available, the use of Norpramin^{R} 100 mg and 150 mg tablets as the appropriate reference products would be acceptable.

The firm submitted comparative dissolution testing results (Table I) between the original formulation and the revised formulation for its desipramine HCl, 100 mg and 150 mg Tablets, respectively. The comparative dissolution were tested at the same time. The firm has compared its desipramine HCl, 100 mg and 150 mg Tablets, lots #95-018T and 95-019T, respectively, (the revised formulations) versus desipramine HCl, 100 mg and 150 mg Tablets, lots #90-023T and 90-022T (the original formulations), respectively.

Reply to Comment

The firm's response to the comment is acceptable.

III. Recommendations:

1. The dissolution testing conducted by Sidmak Laboratories, Inc., on its desipramine HCl, 100 mg and 150 mg Tablets lot #95-018T and 95-019T, respectively, is acceptable. Waivers of in vivo bioequivalence study requirements for the test products are granted. From the bioequivalence point of view, the Division of Bioequivalence deems Sidmak's revised desipramine HCl, 100 mg and 150 mg Tablets to be bioequivalent to the firm's previously approved desipramine HCl, 100 mg and 150 mg Tablets, respectively.

2. The dissolution testing should be incorporated into the firm's

manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1N hydrochloric acid at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following USP specifications:

> Not less than of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

The firm should be informed of the above recommendations.

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRF Date: 3/20/97

Concur: [signature] Date: 3/24/97
for Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

MMakary/3-20-97 wp 71803D.397
cc: ANDA #71-803, 71-804, original, HFD-658 (Makary), Drug File, Division File.

Table I In Vitro Dissolution Testing

Drug (Generic Name): Desipramine HCl
Dose Strength: 100 mg and 150 mg Tablets
ANDA No.:71-803, 71-804
Firm: Sidmak Laboratories, Inc.
Submission Date: March 5, 1997
File Name: 71803D.397

I. Conditions for Dissolution Testing:

USP 23 Basket: Paddle:X RPM: 50
No. Units Tested: 12 Tablets
Medium:900 mL of 0.1N HCl
Specifications: NLT of the labeled amounts of Desipramine is dissolved in 60 minutes.
Reference Drug: Norpramin
Assay Methodology:

II. Results of In Vitro Dissolution Testing: Desipramine

Sampling Times (minutes)	Test Product Lot # 95-018T Strength(mg) 100			Reference Product Lot # 90-023T Strength(mg) 100		
	Mean %	Range	%CV	Mean %	Range	%CV
15	84		15.1	84		10.7
30	101		2.6	101		3.0
45	102		1.2	102		1.9
60	102		1.0	102		2.0

Sampling Times (minutes)	Test Product Lot # 95-019T Strength(mg) 150			Reference Product Lot # 90-022T Strength(mg)150		
	Mean %	Range	%CV	Mean %	Range	%CV
15	23		72.5	51		12.7
30	71		15.3	92		7.8
45	93		4.1	96		4.8
60	98		3.5	97		3.4